Aspergillus Mural Endocarditis

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Walsh, Thomas J., and Hutchins, Grover M.: Aspergillus mural endocarditis. Am J Clin Pathol 71: 640–644, 1979. Infectious mural endocarditis is uncommon and not well documented. The clinical setting and pathologic features of five patients with Aspergillus mural endocarditis are described. Leukemia, carcinoma, renal transplantation, and hepatic failure were the primary diseases. Associated conditions include high-dose corticosteroids, cytotoxic therapy, renal failure, gram-negative sepsis, and endotracheal intubation. All patients received prolonged antibiotic therapy or treatment with three or more antibiotics. All had clinically undetected aspergillosis and severe fungal pneumonia. Fungal myocardial abscesses were present in each patient. Aspergillus mural endocarditis developed in more than 40% of patients with cardiac aspergillosis. Endocardial vegetations were contiguous with underlying myocardial infection; yet they may develop initially as a subendocardial focus rather than from a myocardial abscess. Aspergillus mural endocarditis progressed to destroy the mitral valve ring and served as a source of mycotic embolization to vital organs. (Key words: Aspergillus: Mural endocarditis.)

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ASPERGILLUS, an increasingly frequent cause of infection among debilitated patients,[12,28] has been reported to occur as a cause of infective mural endocarditis in only three patients[3,5,27] since 1947. Since the clinical setting, consequences, and pathogenesis of infective mural endocarditis, especially when caused by Aspergillus, are not understood[17] we studied the clinical and pathologic features of five cases of Aspergillus mural endocarditis.

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Report of Five Cases

As summarized in Table 1, the principal clinical diagnoses of the patients were colonic adenocarcinoma, leukemia, fulminant hepatitis, and rejection of renal transplant. Prolonged antibiotic therapy or (>10 days) treatment with three or more antibiotics or both, were administered to all patients. High-dose corticosteroid therapy was administered to four patients; three of these received concomitant cytotoxic agents. Renal failure complicated the courses of four patients; two underwent endotracheal intubation. Sepsis occurred in two patients, one of whom received amphotericin B and 5-fluorocytosine for candidiasis, which clinically obscured a more aggressive aspergillosis.

All patients were febrile. None had a new murmur. One patient had a vesiculopapular rash from which Candida was cultured. All cultures were negative for Aspergillus. Leukocytosis (16,000–24,000 cells/cumm) with a shift to the left was present in three patients; neutropenia due to cytotoxic therapy occurred in two patients. The only electrocardiographic changes were nonspecific ST-segment and T-wave abnormalities in three patients. Roentgenograms of the chest demonstrated progressive infiltrates in three patients. Seen retrospectively, these infiltrates were consistent with acute pulmonary aspergillosis. A necrotizing Aspergillus pneumonia was demonstrated at autopsy and was a possible portal of entry in all patients.

Table 1. Pertinent Comparative Clinical Findings in Aspergillus Mural

	Age (Years), Sex	Principal Clinical Diagnosis	Fever	Chest Radiograph	Antifungal Therapy	Multiple and/or Prolonged Antibiotics
Patient 1	52, M	Colonic adenocarcinoma	+	Pleural effusion	–	Prolonged
Patient 2	59, M	Acute monocytic leukemia	+	Widespread infiltrates	–	Prolonged
Patient 3	9, M	Fulminant hepatitis	+	Lower lobe infiltrates	–	Prolonged
Patient 4	16, F	Myelomonocytic leukemia	+	Congestive heart failure	+	Prolonged Multiple
Patient 5	29, F	Renal transplantation	+	Widespread infiltrates	–	Multiple

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Table 2. Pertinent Pathologic Findings in Aspergillus Mural Endocarditis

	Age (Years); Sex	Culture for Aspergillus	Mural Vegetations†	Myocardial Abscesses†	Extracardiac Involvement by Fungi	Immediate Cause of Death
Patient 1	52, M	–	LA and MV ring	LV, LA	Lungs, kidneys	Gram-negative sepsis
Patient 2	59, M	–	RA, LV	RA, LV	Lungs, brain, kidneys, liver, spleen, pancreas, thyroid	Disseminated aspergillosis
Patient 3	9, M	–	LV	LV	Lungs, brain, kidneys, liver, spleen, thyroid, pancreas	Gastrointestinal hemorrhage
Patient 4	16, F	–*	RV, LV	RV, LV	Lungs, brain, eyes, spinal cord, kidneys, spleen, thyroid, skin, intestines	Pulmonary hemorrhage
Patient 5	29, F	–	RA, RV, LV	RA, RV, LA, LV	Lungs, trachea, brain, eyes, liver, spleen, thyroid, intestines, pleura, peritoneum	Pulmonary septic emboli

* Culture of cutaneous lesions and cerebrospinal fluid grew *Candida tropicalis*.

† LA = left atrium; LV = left ventricle; MV = mitral valve; RA = right atrium; RV = right ventricle.

Widespread myocardial abscesses were present in all hearts as a component of systemic mycosis. Endocardial and myocardial lesions contained fungal forms characteristic of Aspergillus with large septate hyphae and angular dichotomous branching (Fig. 1). Mural endocarditis arose from myocardial abscesses in two hearts and from an endocardial or subendocardial source in two other hearts. The severe endocardial and myocardial necrosis in the heart of Patient 1 prevented determination of the lesion's origin.

The left atrial–mital ring lesion (Fig. 2) developed independently of any extension from a pulmonary abscess via the pulmonary veins. The mural endocardial lesions appeared as yellow to grayish white excrescences 0.1 mm to 10 mm in greatest diameter, with a mean size of 1 mm to 2 mm in diameter. Aspergilli abounded with virtually no inflammatory infiltrate in patients treated with cytotoxic agents. This reaction was unlike the marked inflammatory response to Aspergillus in those who received no cytotoxic agents.

Extracardiac infection most frequently involved the lungs, brain, and kidney; mycotic abscesses in these organs were common (Fig. 3). Embolic occlusion of major systemic arteries did not occur. However, Aspergilli did invade pulmonary vessels and caused thromboembolic pulmonary arterial occlusion with hemorrhagic infarction.

Endocarditis

Cortico-steroids	Cytotoxic Therapy	Underlying Conditions
—	—	Renal failure, endotracheal intubation, gram negative sepsis, GI surgery ×2
+	+	–
+	–	Renal and hepatic failure
+	+	Acute renal failure, Candida sepsis
+	+	Meningitis, endotracheal intubation, transplant nephrectomy for rejection

Death of one patient was ascribed to Aspergillus pneumonia and intrapulmonary hemorrhage. Immediate causes of death in other patients were related to gram-negative sepsis, massive gastrointestinal hemorrhage, Aspergillus sepsis, acute renal failure, and septic pulmonary emboli with hemorrhagic infarction.

Discussion

True mural endocarditis without a known antecedent endocardial lesion[17] has been reported to occur in 22 patients.[3–6,8–11,17–21,23,24,26,27] Eight instances were due to fungi, and three were caused by Aspergillus.[3,5,27]

Other mechanisms of mural endocarditis include infection of right mural endocardium injured by jet flow through a ventricular septal defect,[7] infection of preexistent ventricular aneurysm,[16] endocarditis on an auricular septal defect,[1] infectious thrombosis of a central venous catheter,[2] infection of mural thrombus overlying a myocardial infarct,[13] complication of cardiac pacemaker[22] and mural bacterial endocarditis of a ventricular friction lesion.[15]

Mural endocarditis is usually not the cause of death. However, it has caused myocardial rupture resulting in aortico–right ventricular fistula[26] and aortico–left atrial fistula.[21] Embolization has caused sudden cerebrovascular accident[23] and peripheral arterial occlusion by Pseudomonas-laden emboli.[21]

Three cases of mural endocarditis due to Aspergillus have been previously reported. The five patients described here were encountered among the 13 with aspergillosis of the heart studied by autopsy at The Johns Hopkins Hospital.[25] The lesions develop in the clinical setting of severely debilitating diseases. Impairment of the host's defenses against Aspergillus occurred by (1) prolonged treatment with multiple and broad-spectrum antibiotics, which altered normal bacterial flora, (2) cytotoxic therapy and corticosteroids, (3)

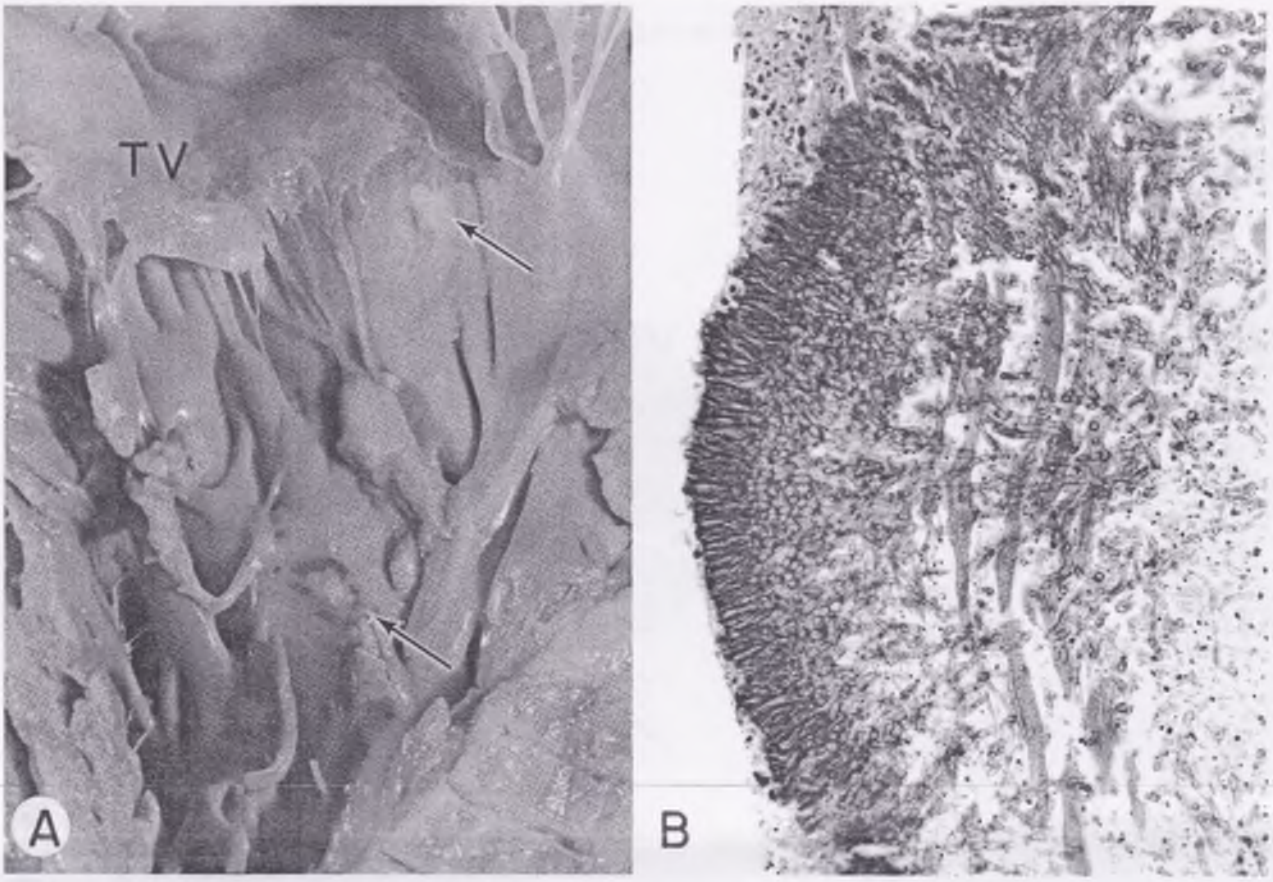

FIG. 1. *A*: Endocardial lesions (*arrows*) on the right ventricular endocardium. TV-tricuspid valve. *B*: Aspergillus growing in the endocardium and destroying the immediately subjacent myocardial muscle cells. The organisms have branching septate hyphae. Hematoxylin and eosin. ×250.

endotracheal intubation, (4) uremia, (5) gram-negative sepsis, and (6) repeated surgical procedures. The classic manifestations of endocarditis, such as new murmur, Osler nodes, Roth spots, splinter hemorrhages, and petechiae, were not seen in these patients with Aspergillus mural endocarditis.

Abrupt embolic occlusion of large peripheral arteries, which is a characteristic of vegetative fungal valvular endocarditis,[14] was generally not observed in Aspergillus mural endocarditis. Instead, these endocardial lesions usually developed in the setting of widespread aspergillosis. Embolic myocardial abscesses may rupture into the endocardium.[3,5] Other lesions seem to arise from a subendocardial focus and without any significant myocardial involvement.

Most lesions are small and do not develop into large mural vegetations, since the more overwhelming underlying disease and generalized mycosis cause the early demise of these patients. The smaller vegetations aggravate the clinical condition by serving as sources of microemboli, which may develop as major abscesses, especially in brain and lung. The Aspergillus mural lesions also invade and destroy the myocardial wall and may lead to cardiac rupture. Aspergillus mural endocarditis generally occurs in the debilitated patient as part of a generalized mycosis, is difficult to diagnose, is usually not the cause of the patient's demise, but may cause widespread myocardial necrosis and serve as a source of mycotic emboli.

References

1. Abbott OA: Vegetative endocarditis in an auricular septal defect. Am Heart J 21:807–810, 1944
2. Becker AE, Becker MJ, Martin FH, et al: Bland thrombosis and infection in relation in intracardiac catheter. Circulation 46:200–203, 1972
3. Buchbinder NA, Roberts WC: Active infective endocarditis confined to mural endocardium. Arch Pathol 93:435–440, 1972
4. Cates JE, Christie RV: Subacute bacterial endocarditis. A review of 442 patients treated in 14 centres appointed by the Penicillin Trials Committee of the Medical Research Council. Q J Med 20:93–130, 1951
5. Cawley EP: Aspergillosis and the aspergilli. Report of a unique case of the disease. Arch Intern Med 80:423–434, 1947
6. Chance EJ: Rare case of abscess of the heart, and account of the postmortem appearances; with remarks. Lancet 1:548–550, 1846
7. Eigen LA, Abel AR: Subacute bacterial endocarditis on the right ventricular wall opposite a ventricular septum defect. Am J Med Sci 202:207–211, 1941

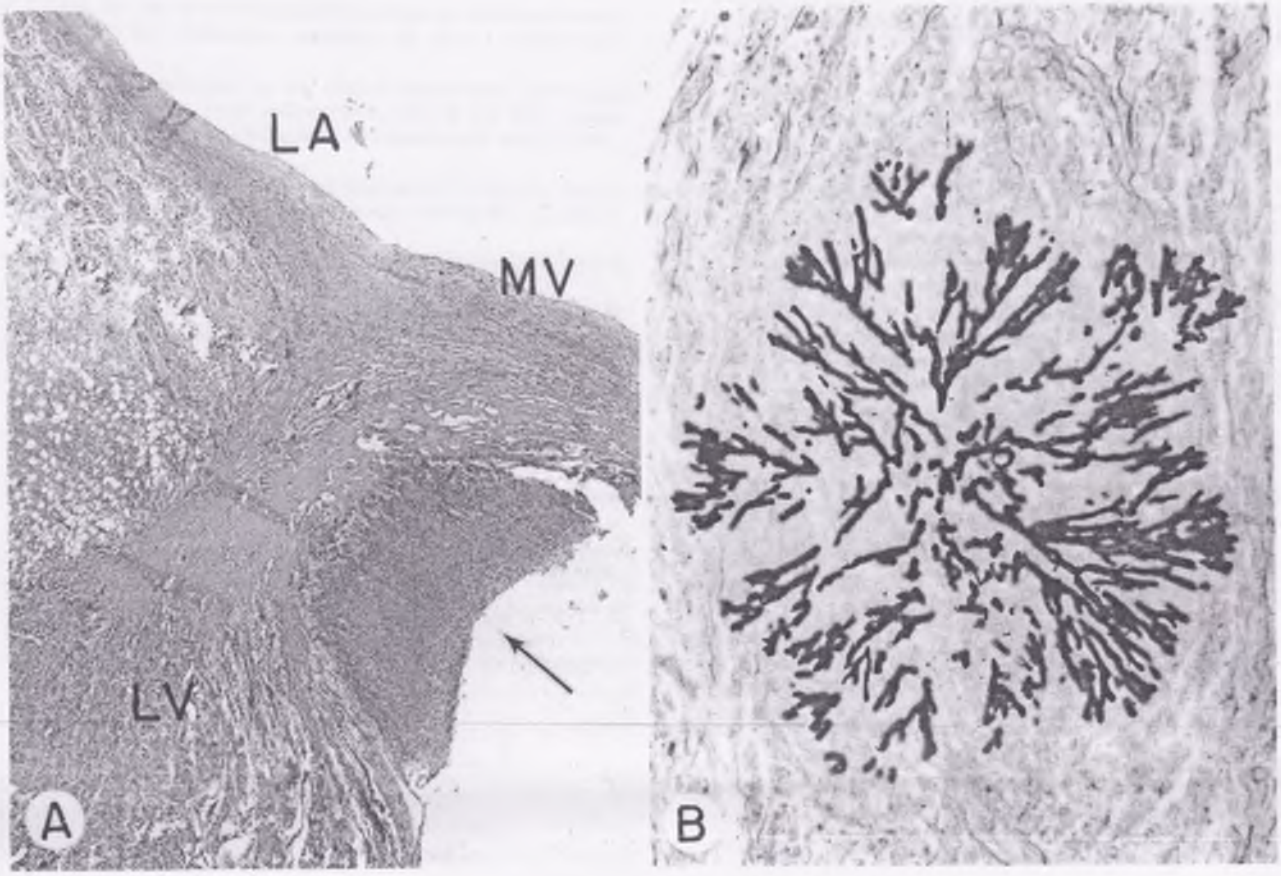

FIG. 2. *A*: Aspergillus endocarditic lesion (*arrow*) beneath the mitral valve (MV). The inflammatory reaction extends to the epicardium. LA-left atrium; LV-left ventricle. Hematoxylin and eosin. ×15. *B*: Colony of Aspergilli which has provoked a relatively mild inflammatory response. Methenamine silver. ×300.

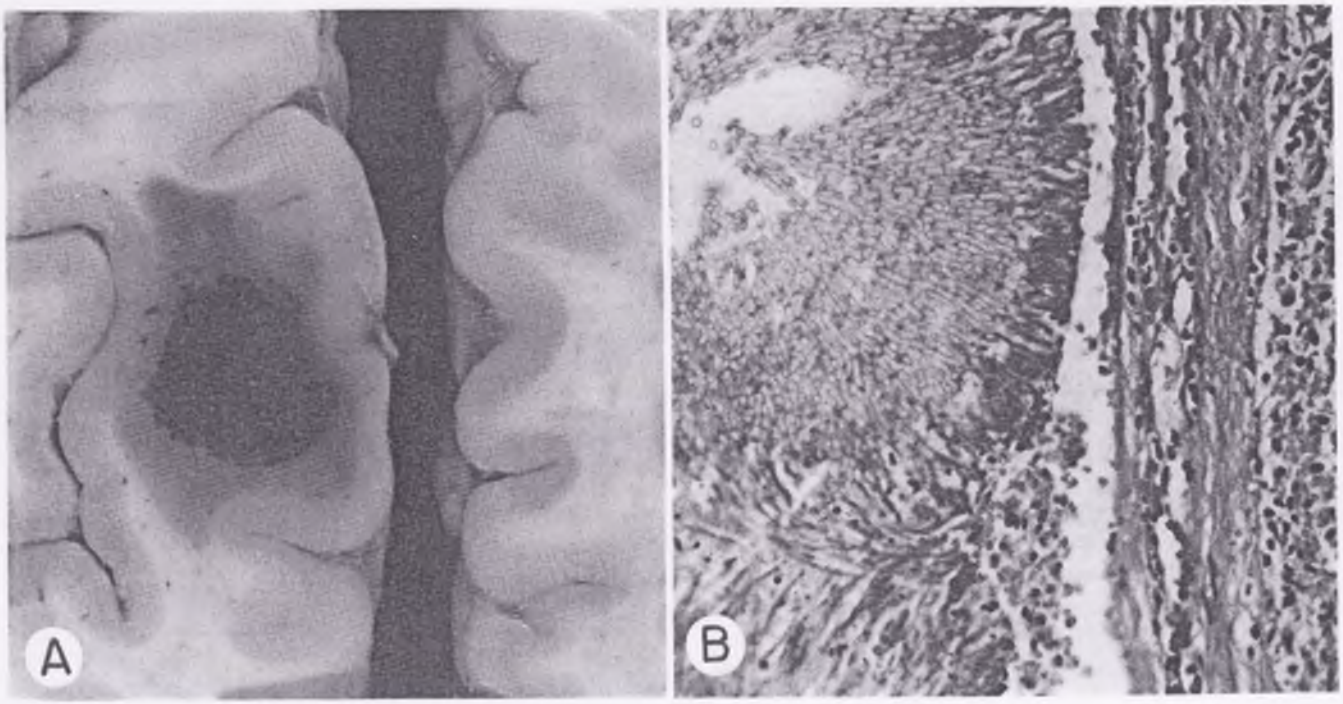

FIG. 3. *A*: Cerebral abscess produced by Aspergillus presumably embolic from an endocarditis. *B*: Aspergillus embolus in a small splenic artery. The arterial wall (*right*) shows severe inflammation. Giemsa. ×250.

8. Gorlin R, Favour CB, Emery FJ: Long-term follow-up study of penicillin-treated subacute bacterial endocarditis. N Engl J Med 242:995–1001, 1950
9. Hirsch EF: Septic thrombophlebitis of the leg with mural endocarditis and pulmonary embolism. Ill Med J 114:289–292, 1958
10. Horder T: Discussion on the clinical significance and course of subacute bacterial endocarditis, held at the 88th Annual Meeting of the British Medical Association. Br Med J 2:301–304, 1920
11. Howitt T: Remarkable cause of abscess of the heart. Pain in the leg the only symptom of disease during life. Lancet 1: 684–685, 1846
12. Hughes WT: Fatal infections in childhood leukemia. Am J Dis Child 122:283–287, 1971
13. Joffe S, Feil H: Subacute bacterial endocarditis arising in mural thrombi following a myocardial infarction: A case report. Circulation 12:242–246, 1955
14. Kammer RB, Utz JP: Aspergillus species endocarditis: The new face of a not so rare disease. Am J Med 56:506–521, 1974
15. Kuhn C III: Mural bacterial endocarditis of a ventricular friction lesion. Arch Pathol 95:92–93, 1973
16. McNally EM, Kennedy RJ, Grace WR: Salmonella infantis infection of a pre-existent ventricular aneurysm. Am Heart J 68:541–548, 1964
17. Milstoc M, and Berger AR: True bacterial mural endocarditis. Chest 59:103–105, 1971
18. Moxon W: Case of abscess of the heart bursting into the left ventricle. Trans Pathol Soc London 20:113–114, 1869
19. Nushan H, Sawyer CG, Rogers RO, et al: Bacterial endocarditis due to salmonella typhimurium. Am J Cardiol 7:608–612, 1961
20. Persaud V: Two unusual cases of mural endocarditis, with a review of the literature. Am J Clin Pathol 53:832–838, 1970
21. Reyes MP, Palutke WA, Wylin RF, et al: Pseudomonas endocarditis in the Detroit Medical Center 1969–1972. Medicine 52:173–194, 1973
22. Schwartz IS: Bacterial endocarditis associated with a permanent transvenous cardiac pacemaker. JAMA 218:736–737, 1971
23. Taniguchi T Murphy FD: Mural bacterial endocarditis produced by proteus. JAMA 143:427–428, 1950
24. Trasoff A, Meranze DR: The association of acute interstitial pancreatitis with acute pneumococcic mural endocarditis. J Lab Clin Med 29:590–594, 1944
25. Walsh TJ, Hutchins GM, Bulkley BH, et al: Fungal infections of the heart: Clinical and pathologic study of 47 patients (abstract) Lab Invest 38:371, 1978
26. Weiss S, WIlkins RW: Myocardial abscess with perforation of the heart. Am J Med Sci 194:199–205, 1937
27. Welsh RA, Buchness JM: Aspergillus endocarditis, myocarditis and lung abscesses. Report of a case. Am J Clin Pathol 25: 782–786, 1955
28. Young RC, Bennett JE, Vogel CL, et al: Aspergillosis. The spectrum of the disease in 98 patients. Medicine 49:147–173, 1970